REMARKS

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification

The Examiner asserted that the title of the application was not descriptive. Applicants have amended the title to address the Examiner's concerns.

The Examiner also requested that Applicants provide a paper copy of the Sequence Listing with the present response. Applicants provide the requested paper copy of the Sequence Listing herewith.

Information Disclosure Statement

The Examiner requested that Applicants provide further information regarding the BLAST results included in the Information Disclosure Statement submitted Sept. 12, 2002. Applicants submit herewith a new Information Disclosure Statement providing the publication dates of the sequences identified in the BLAST search.

Priority

The PTO has stated that because the claimed nucleic acids have no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, U.S. Application 09/403297, filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. §119 to U.S. Provisional Application 60/105000 filed 10/20/1998.

Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility. The sequences of SEQ ID NO: 117 and SEQ ID NO:

118 were first disclosed in Figure 1 and Figures 2A-C of US Provisional Application 60/105000 filed 10/20/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-6, 8-10 and 14-20 were rejected as being indefinite because the protein of SEQ ID NO: 118 was not disclosed as being expressed on a cell surface. Accordingly, the Examiner asserts that the claim limitations relating to the "extracellular domain" are indefinite. The features described in Figure 118 for SEQ ID NO: 118 indicate that there is a signal peptide at amino acids 1-23, transmembrane domains at amino acids 81-100, 121-141, and 173-194. Accordingly, the extracellular domains lie at amino acids 24-80 and amino acids 142-172. Applicants have amended the claims to provide the locations of the extracellular domains.

Limitations relating to the "extracellular domain..lacking its associated signal sequences" were also asserted to be indefinite. In the interest of advancing prosecution of this application, Applicants will acquiesce to the PTO's assertion that a signal peptide is not normally considered part of the extracellular domain. By making this concession, Applicants understand that element (c) of Claims 1-6 and 14, as well as Claim 9, describes a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 118, **lacking** its associated signal peptide. At the same time, as amended, element (d) of Claims 1-6 and 14, as well as Claim 10, describes a nucleic acid sequence encoding the extracellular domain of the polypeptide of SEQ ID NO: 118, **including** its associated signal peptide. Applicants state that this argument is made only in connection with the instant application, and does not reflect the Applicants' interpretation of any claims in any related applications.

Claims that recite that the claimed polynucleotide "hybridizes to" another sequence, such as Claim 14, were also rejected as being indefinite. Claim 15 was also asserted to be indefinite in reciting "stringent" hybridization conditions. Claim 15 was rejected as being dependent on rejected Claim 14. Applicants have amended Claim 14 to recite particular hybridization conditions and Claim 15 has been canceled. Applicants maintain that the amended claims meet the requirements of 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-20 as lacking a specific, substantial, and credible utility. The PTO asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1572. One of the asserted utilities for the claimed nucleic acids is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1572 cDNA is more highly expressed in normal lung tissue compared to lung tumor. The PTO has rejected this utility because there is no supporting evidence to indicate that the polypeptide encoded by the claimed nucleic acids of the instant invention is more highly expressed in normal tissue compared to tumor. The PTO also asserts that the evidence that the polynucleotide is more highly expressed in normal lung compared to lung tumor is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to lung tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the polynucleotides for diagnostic or therapeutic purposes. The PTO also states that the specification does not disclose a correlation between any specific disorder and the altered level of the claimed nucleic acids encoding the polypeptides. The PTO also states that because cancerous tissue is aneuploid, the data is unreliable. Finally the PTO argues that there is no correlation between protein expression and nucleic acid levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic

quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the

burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO1572 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO1572 polypeptide in normal lung tissue compared to lung tumor is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to lung tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. Applicants also address the PTO's argument that because cancerous tissue is aneuploid, the data is unreliable. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids related to the gene encoding the PRO1572 polypeptide.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states

that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 8. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the claimed nucleic acids, or their corresponding polypeptides, whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding PRO1572 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal lung tissue compared to lung tumor, respectively, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO acknowledges that if the PRO1572 protein has utility, then this confers utility on the polynucleotide encoding the protein. Office Action at 7. However, the PTO argues that there is no supporting evidence that the polypeptide encoded by the polynucleotide of the instant invention is more highly expressed in normal lung tissue compared to lung tumor. The PTO also

states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that one cannot extrapolate the expression data provided in the specification to support the implicit assertion that the polynucleotides encoding PRO1572 can be used in cancer diagnosis or therapy.

Applicants submit that those of skill in the art would recognize that amplification of a gene due to aneuploidy will more likely than not lead to an increase in expression of that gene as measured by the level of mRNA. This assertion is supported by numerous references. Orntoft *et al.* (*Molecular and Cellular Proteomics*, 1:37-45 (2002)) (submitted herewith as Exhibit 2) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (Orntoft at 37, column 1, abstract). In addition, Hyman *et al.* (*Cancer Research*, 62:6240-6245 (2002)) (submitted herewith as Exhibit 3) used CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines. They showed that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (Hyman at 6244, column 1, last paragraph).

Additional supportive teachings are also provided by Pollack *et al.* (*PNAS*, 99:12963-12968 (2002)) (submitted herewith as Exhibit 4) who studied a series of primary human breast tumors and found that "[b]y analyzing mRNA levels in parallel, we have also discovered that *changes in DNA copy number have a large, pervasive, direct effect on global gene expression patterns* in both breast cancer cell lines and tumors." (Pollack at 12967 at column 1, emphasis added). Their study found that "62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack at 12963, column 1, abstract). This report is particularly persuasive because the high-resolution comparative genomic hybridization analysis used to assess DNA copy number was particularly sensitive.

Together, these articles collectively teach that in general, gene amplification increases mRNA expression. As discussed below, it is also the established general rule in the art that the level of protein expression is directly related to the level of gene expression, so that increased gene expression leads to increased protein expression.

Relying on a single example of one gene, the PTO states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8-9. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding PRO1572 in normal lung tissue compared to lung tumor. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA. Applicants respectfully submit that by relying on Pennica, the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation

between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 5). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. The statements of Grimaldi and Polakis are supported by the

teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 7. Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1572 mRNA is expressed at a higher level in normal lung tissue compared to lung tumor, the PRO1572 polypeptide will also be expressed at a higher level in normal lung tissue compared to lung tumor. One of skill in the art would recognize that a nucleic acid encoding a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool.

Applicants submit that they have therefore established two separate basis for utility of the claimed nucleic acids. The first argument is based on the differential expression of the PRO1572 encoding gene in normal lung tissue compared to lung tumor. The second argument is based on the utility of the PRO1572 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression. As the PTO acknowledges, the utility of the polypeptide confers utility on the encoding gene as well.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1572, which Applicants submit is not true, a polypeptide encoded by

a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 5, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 8), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 9). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would the nucleic acid which encodes it. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease of condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1572. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1572 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO1572 polypeptide is more highly expressed in normal lung tissue compared to lung tumor. These data are strong evidence that the gene encoding the PRO1572 polypeptide is associated with lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the gene encoding PRO1572 with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly lung tumor, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1572 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed nucleic acids cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1572 gene in normal lung tissue compared to lung tumor, are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools. Applicants have also shown that whether the differential expression of the PRO1572 gene is due to aneuploidy or not does not affect its usefulness as a diagnostic tool.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO1572 protein has utility as a diagnostic tool for cancer, and as the PTO acknowledges, nucleic acids encoding the polypeptide also have utility as a result.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility because there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature associated with PRO1572. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO1572 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO1572 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled. The PTO also states that even if a specific and substantial utility were established, they are enabled only for polynucleotides of SEQ ID NO: 117 and fragments that are usable as hybridization probes, they are not enabled for claims to polynucleotides with 80-99% sequence identity to SEQ ID NO: 117, those which encode polypeptides with 80-99% sequence identity to SEQ ID NO: 118, or those which hybridize to any of the above because there is no structural or functional information provided in the specification. The PTO states that there is insufficient guidance regarding how to make PRO1572 polynucleotide variants. The PTO also states that the hybridization claims are not enabled because they do not recite that the polynucleotide encodes a protein having a specifically disclosed activity. The PTO next asserts that even if utility of the claimed nucleic acids as hybridization probes is established, degenerate sequences are not enabled.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

The PTO asserts that even with an established utility, only polynucleotides of SEQ ID NO: 117 are enabled because there is no structural or functional information provided. Applicants have amended the claims to incorporate the limitation that the claimed nucleic acids with less than 100% identity to SEQ ID NO: 117, or which encode a protein with less than 100% identity to SEQ ID NO: 118, must be more highly expressed in normal lung tissue compared to lung tumor respectively, or encode a polypeptide that is more highly expressed in normal lung tissue compared to lung tumor. Applicants assert that techniques used to make variants of polynucleotide or polypeptide sequences are well-known to those of skill in the art (see, e.g., paragraph [0258] of the specification). Thus, the claims as amended contain sufficient structural information to enable the claims.

Applicants respectfully disagree that the hybridization claims are not enabled. First, Applicants assert that those of skill in the art are well aware of which sequences will hybridize under various hybridization conditions. This is especially true as Applicants have amended the claims to include specific conditions under which the claimed hybridization occurs. Applicants submit that by disclosing the sequence of the target nucleic acid along with the specific hybridization conditions, Applicants have disclosed sufficient structural information about the claimed nucleic acids such that those of skill in the art would know how to make them. Second, Applicants submit that undue experimentation would not be required to use the claimed nucleic acids as diagnostic tools. The level of skill in the art is high, and methods of using nucleic acid sequences as probes are well-known and well-established in the art. One of skill in the art would know how to use the claimed nucleic acids, for example, as hybridization probes for the diagnosis of cancer as outlined in the specification at, for example, paragraph [0336], and Example 18 beginning at paragraph [0529].

Finally, Applicants note that because they have established a utility for the PRO1572 polypeptide, supported by the declarations of experts in the field and several references, polynucleotides which encode the PRO1572 polypeptide also have utility. This includes degenerate polynucleotide sequences which encode the PRO1572 polypeptide. Therefore, contrary to the PTO's assertion, polynucleotides that differ from SEQ ID NO: 117 due to codon degeneracy are enabled.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected of Claims 1-5 and 15-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polynucleotides encode a particular protein, or that any encoded protein possess any particular biological activity, the claims fail the written description requirement.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns nucleic acids having a specified sequence identity with the disclosed polynucleotide sequence of SEQ ID NO: 117, or encoding a polypeptide with the specified polypeptide sequence of SEQ ID NO: 118, and as amended, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in normal lung tissue compared to lung tumor, or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal lung tissue compared to lung tumor respectively". Other claims relate to nucleic acids which hybridize to nucleic acids of SEQ ID NO: 117, or polynucleotides which encode a polypeptide of SEQ ID NO: 118, under the

specified stringent conditions. Based on the detailed description of the cloning and expression of variants of PRO1572 in the specification, the description of the gene expression assay, the actual reduction to practice of sequences SEQ ID NOs: 117 and 118, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejects Claims 1-10 and 12-20 as being anticipated by Sheppard et al. (WO 00/15659A2, published March 22, 2000). The Examiner asserts that Sheppard et al. disclose an amino acid sequence with 100% identity to SEQ ID NO: 118 and also describes the full length coding cDNA.

As discussed above, the sequences of SEQ ID NO: 117 and SEQ ID NO: 118 were first disclosed in Figure 1 and Figures 2A-C of US Provisional Application 60/105000 filed 10/20/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Accordingly, Applicants maintain that WO 00/15659A2, which was published March 22, 2000, is not prior art under 35 U.S.C. §102(b) since its publication date is not more than 1 year prior to Oct. 20, 1998. Even should the Examiner assert that the present application is not entitled to a priority date earlier than August 24, 2000, the cited PCT application would not be prior art under 35 U.S.C. §102(b).

Applicants note that WO 00/15659 does not constitute prior art under 35 U.S.C. §102(a). In view of the fact that WO 00/15659 published on March 23, 2000, neither WO 00/15659 nor its priority application, U.S. Patent Application Serial No. 09/154,444 were publicly accessible as of October 20, 1998 (the filing date of the earliest application to which the present application claims priority).

Furthermore, Applicants note that as of March 23, 2000, the publication date of WO 00/15659, Applicants were in possession of so much of the invention as is disclosed in WO 00/15659. Applicants first disclosed the sequences of SEQ ID NO: 117 and SEQ ID NO: 118 in U.S. Provisional Application 60/105000 filed Oct. 20, 1998. As Oct. 20, 1998 date precedes the

March 23, 2000 publication date of WO 00/15659, Applicants have shown possession of the claimed invention prior to WO 00/15659.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited reference. While WO 00/15659 discloses the sequence of SEQ ID NO: 118 and provides tissue distribution data for the corresponding transcript, WO 00/15659 does not correlate the protein with any particular disease or physiological function. Applicants demonstrated, by means of the disclosure in their provisional application filed October 20, 1998, that they were in possession of so much of the claimed invention as disclosed WO 00/15659. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102 be withdrawn.

Furthermore, Applicants note that neither W0 00/15659 nor U.S. Patent Application Serial No. 09/154,444 constitute prior art under 35 U.S.C. §102(e). In particular, it is Applicants understanding that U.S. Patent Application Serial No. 09/154,444 is abandoned and that no applications claiming priority to it are pending in the U.S.P.T.O. Furthermore, because WO 00/15659 was filed prior to November 29, 2000, its effective filing date under 35 U.S.C. 102(e) would be the date that it completed the requirements for entry into the U.S. National Phase. It is Applicants understanding that WO 00/15659 did not enter the U.S. National Phase.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

Conclusion

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Dec. 16, 2004

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 30,313
(619) 235-8550

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DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.